HYPOPARATHYROIDISM DIAGNOSED BY NEUROLOGICAL SIGNS AND WIDESPREAD INTRACEREBRAL CALCIFICATIONS

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ABSTRACT

Neurological signs associated with intracerebral calcifications require a complex management of calcium, phosphate and parathormone levels and search of a series of general and cerebral disease too. The mechanisms of intracerebral calcification in hypoparathyroidism are not completely known. Neurological signs associated with intracerebral calcification are very rarely the presenting symptoms of hypoparathyroidism. We present 2 cases in which the diagnosis of hypoparathyroidism was brought on by several neurological signs and widespread intracerebral calcification.

Key words: intracerebral calcification, hypoparathyroidism

INTRODUCTION

Neurological signs together with intracerebral calcification as presenting symptoms in hypoparathyroidism are an extremely rare situation.

The clinical picture which points to a parathormone (PTH) deficiency usually consists in the common signs of spasmofilia (muscular cramps, Cvosteck and Trousseau signs, paresthesia, hyperexcitability, fatigue, anxiety) (1,2, 3, 4).

The following neurological signs may also be present: extrapyramidal signs (coreoathetosis, parkinsonian syndrome, dystonia, hemibalismus, and oculogiric crisis), epilepsy, spastic paraparesis, ataxia, dysarthria, dysphagia, papillary oedema. Psychiatric features are: anxiety, emotional lability, depression, confusion, hallucination, psychosis (4, 5).There has also been described: cataracts, abnormalities of dentition, dry skin, congestive heart disease, QT prolongation (4).

The mechanism of intracerebral calcification in hypoparathyroidism is not completely known.

Hyaline degeneration, calcifications in media and adventitia of the arterioles (5) have been described. The phenomenon looks like being directly linked to abnormal serum levels of calcium and phosphate. However, CSF calcium and phosphate levels are stable irrespective to an increased or decreased PTH secretion (3).There are studies which suggest that PTH may diffuse straight across the blood brain barrier (BBB) and that it has a direct effect upon cerebral function. A specific action upon certain sites of basal ganglia could be possible. That is why clinical signs may occur in treated patients too (5).

Eaton and Aines (1939), Laser and Wechsler (1960) suggest that cerebral calcifications result from the long standing hypocalcemia which results in abnormalities of calcium metabolism (5).

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Naef and Adle report symmetric bilateral calcification in the basal ganglia (striatum, pallidum). They consist in hyalinosis and calcium deposition in media and adventicea of the small vessels. Severe lesions of the vessels imply degeneration and cell loss in the affected structures.

Calcium is accumulated in the crystalline form of apathyte: 3Ca5 (PO4)2Ca x2, which may present under several forms. In bones apathyte is hydroxiapathyte 3Ca3(PO4)2CaOH2 with a modified composition, certain ions from the surface being substituted (especially calcium may be substituted by phosphate).

Clinical signs are not always present in intracerebral calcification, and hypoparathyroidism is not the only condition which produces such calcifications on the other hand.

Intracerebral calcification is also present in lethargic encephalitis, carbon monoxide intoxication, hypoxia, tuberous sclerosis (5). Neurological signs frequently may be reversible with calcium level normalization, even if structurally the calcification may remain unchanged (1, 2, 3, 4, 5).

The same sort of calcifications occur in pathologic conditions which produce hypocalcemia and hyperphosphatemia like primary, secondary, tertiary (6), or idiopathic hypoparathyroidism or in pseudotumoral generalized calcinosis respectively.

Extensive, pseudotumoral extraskeletal calcifications are frequently found in that case. Calciphylaxis is the term which defines that type of extraskeletal calcifications, consisting basically in middle and small arteries media calcifications with or without intimal proliferation, fibrosis and thrombosis, resulting in ischemia, necrosis and superimposed infection of the skin (8,9,10).

Morphological changes were described by Bryant and White in 1898. The experimental model was realized on nephrectomized rats by Seye in 1962 but clinical implications were reported by Gipstein et al only later in 1976.

The pathogenesis is still obscure; multiple mechanisms resulting in calciphylaxis seem to take place. Multiple intricate pathological factors are present: chronic renal failure, obesity, diabetes, cirrhosis, rheumatoid arthritis, hypercalcemia, hyperphosphatemia, aso. Some cytochemical factors have been identified too.

Molecular and cytochemical factors have been identified as crucial in bone metabolism. The receptor activator of nuclear factor-kB (RANK), RANK ligand, and osteoprotegerin appear to regulate skeletal and extraskeletal mineralization. Uraemia-induced defects in this system may predispose to calciphylaxis. Corticosteroids, aluminium, hyperparathyroidism, liver disease, and a variety of inflammatory processes all can alter this balance and promote vascular calcification. Chronic inflammatory conditions may predispose to calciphylaxis by reducing serum levels of fetuin-A, an important inhibitor of calcification produced in the liver (8).

That type of arterial lesion produces circulatory disturbance resulting in trophic changes and sometimes necrosis, not only, but especially in the skin. The same mechanism could be present inside the nervous system too (8, 9, 10).

We present 2 cases of hypoparathyroidism which were admitted for neurological presenting symptoms.

CASES PRESENTATION

Case no.1

A 76-year-old woman was admitted with left hemibody motor deficit of a sudden onset and speech disturbance. The patient was right-handed; her blood pressure was known to be high and neglected too. She had thyroid surgery more than 20 years ago (neither did she know the name of the thyroid disease, nor did she have any medical paper) and she got Calcium gluconate 1-2 vials/week and did not follow any endocrinological check in the last years. She underwent cataracts surgery 4 and 5 years ago in both eyes. Her family reported that she had had severe dizziness in the last year, difficult gait, muscular cramps, and intermittent tremor of the upper limbs during rest and action, slurred speech, memory impairment and confusional episodes in the last year, but she had refused any kind of medical examination.

On examination we found: a somnolent patient who was not responding to questions. Eye axes were parallel, eye movements and oculocephalic reflexes were normal. The pupils were slightly irregular and eccentric and pupilary light reflex was lost following cataracts surgery.

She had left facial nerve weakness (flattened nasolabial fold and depressed angle of the mouth). She had diminished movements of left limbs and athetosic movements of left upper limb.

Neither standing nor sitting were possible, she fell backwards and towards left. She had bilateral dysmetria, more pronounced on the left side. Deep tendon reflexes (DTR) were exaggerated bilaterally; Babinski sign and palmomental reflex were present bilaterally. A slight extrapyramidal rigidity was bilaterally present. Sensory examination was difficult as she was not very able to cooperate, but

she reacted promptly to painful stimuli, light touch was preserved, she recognized objects placed in the hand with closed eyes, had normal joint position sense and vibratory sensation was normal distally in the lower limbs. Cvostek and Trousseau signs were present.

CT scan disclosed marked cerebral atrophy and multiple symmetric intracerebral calcifications in the cerebellum (in dentate) and in the hemispheres (striatum, periventricular white matter, centrum semiovale, corona radiata, cortex) (fig. 1-6).

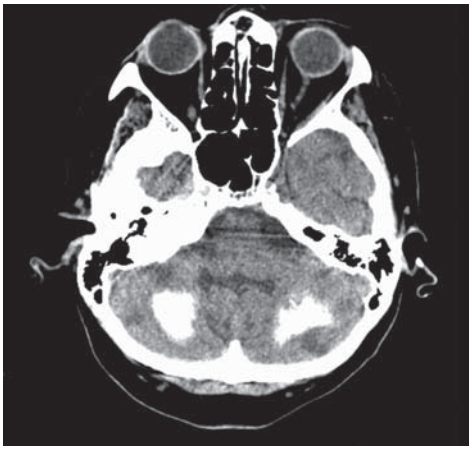


FIGURE 1

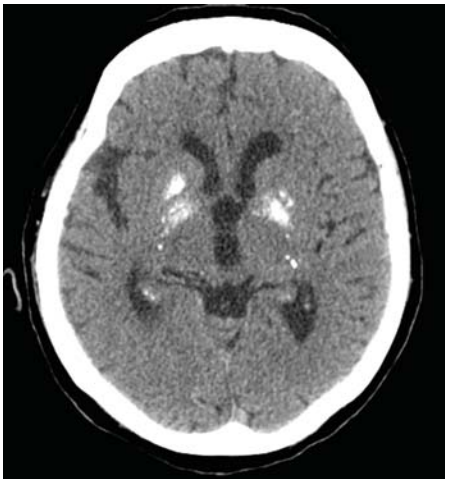
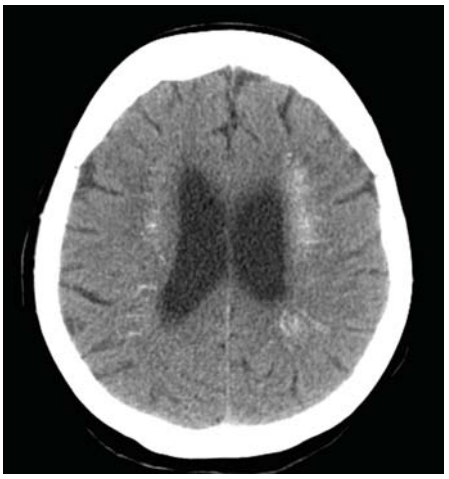


FIGURE 2

FIGURE 3



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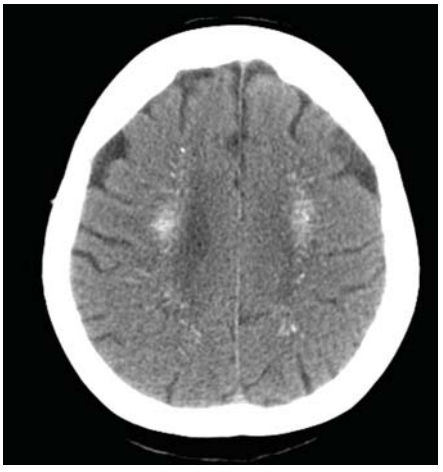

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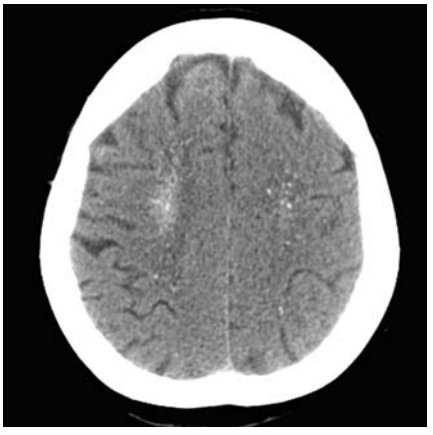


FIGURE 6

An emergency CT scan disclosed marked cerebral atrophy and multiple symmetric intracerebral calcifications in the cerebellum (dentate nuclei) and cerebral hemispheres (basal ganglia, periventricular white matter, centrum semiovale, corona radiata and cortex) (fig. 1-6).

A brain MRI did not disclose additional data.

Laboratory findings consisted in slight elevated ESR (36/60), 14 mg% haemoglobin, 44%

haematocrit 3.800.00 red blood cells, 14.000 white blood cells, 114 mg% blood sugar,106 mg% blood nitrogen urea, 1.4 mg% bilirubinemia, 20 UI/l ASAT, 22 UI/l ALAT, 145 mg% cholesterol, 71 mg% triglycerides, urinary infection.

Serum calcium level was low, 2.5% (normal ranges: 8.6-10.3 mg %), magnesium serum level was normal, 2.55 mg%. Parathormone serum level was undetectable.

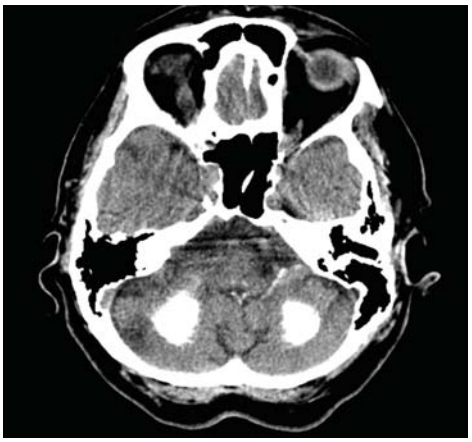
The next days the patient presented fever, bronchitis and renal failure of the prerenal type. Mineral and fluid balance was restored, antibiotics were administered, and calcium and D vitamine were supplied both oral and parenteral.

The general state improved in a few days, she became cooperative at verbal tasks. She still had confusional episodes, the sleep/awake rhythm was disturbed. She was able to sit, but could only walk with support. The left hemiparesis, left upper and intermittently right upper limb athetosic movements, the extrapyramidal rigidity and bilateral dysmetria persisted. Serum calcium level became 7.6 mg% on discharge after 12 days, and the patient was referred to the endocrinological department.

Case no.2

A 72-year-old woman was admitted for right side weakness and language disturbance consisting in expressive aphasia which had developed rapidly in the last 2 days. She had had a right hemiparesis with regressive evolution, without speech disturbance 2 years ago. She was diagnosed with high blood pressure, she had therapeutically controlled values. She was taking antidepressants in the last 10 years. She presented a fall and she broke her pelvic bone 1 year ago. She was on enteric coated Aspirin 75 mg/day, Perindoprile 5 mg/day, Tanakan 40 mg x3/day, Tianeptine 12.5 mg x3 /day, Alprazolam 0.25 mg x3/day. ACT scan at the time of the former admission revealed massive bilateral symmetric calcifications in dentate of the cerebellum, in the deep white matter near anterior horn of the lateral ventricles, and less pronounced calcifications, bilateral symmetric, in the median region of the nucleus lenticularis. Fig. 7-10 she presented a fall breaking her pelvic bone 1 year ago and she was not able to walk afterwards.

The general clinical examination was normal. Neurological examination found a depressive and anxious patient. She had daytime sleepiness and night sleeplessness. Comprehension was good, speech output was only a few words, and she was not able to express sentences. Aphasia with paraphasia was diagnosed. Praxis was difficult to examine



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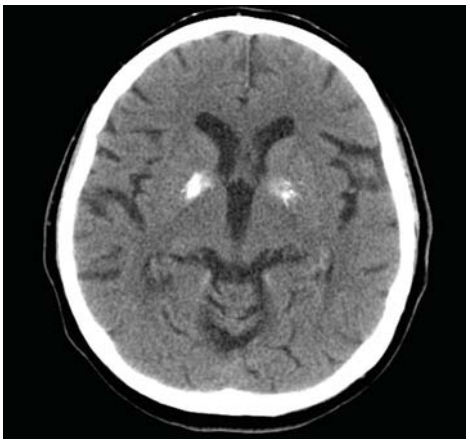

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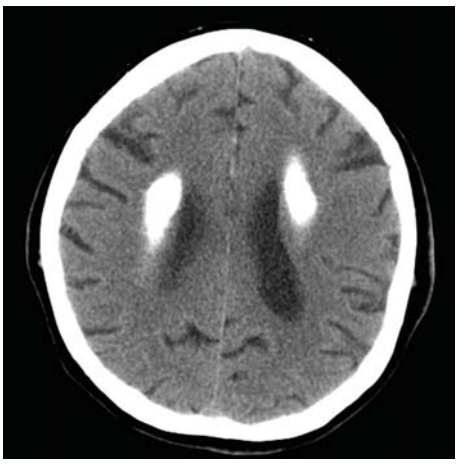

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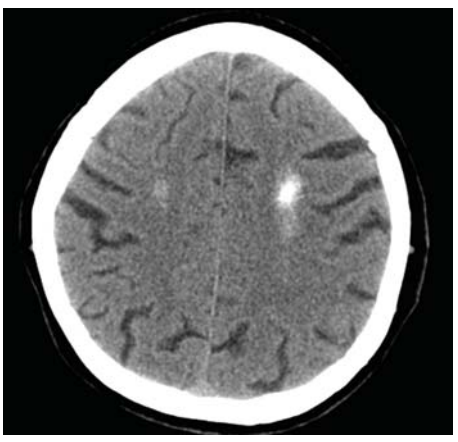
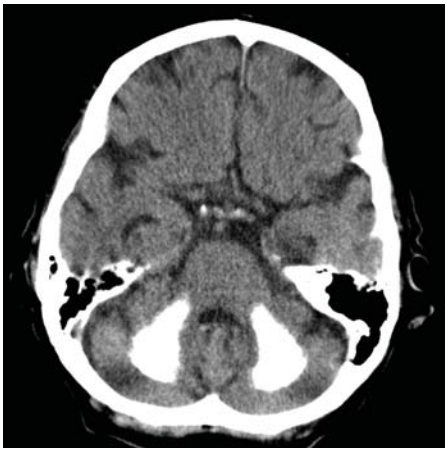


FIGURE 10

because of comprehension impairment, but the patient was able to provide herself with food, to use the plates and dishes, the telephone and the personal hygiene objects in the proper manner. She was not able to dress and could not write because of the motor deficit. She only could read letter by letter. There was a right facial nerve paresis of the central type, right motor deficit (MRS: 3/5 in upper limb, 4/5 in lower limb). Motor deficit predominated distally in the upper limb: she couldn't hold objects, finger movements were only flickered. A slight spasticity in the right limbs was present, DTR were normal; Babinski sign was present on the right.

She presented numbness and decreased sensibility for all sensory modalities on the right hemibody. She was not able to stand; she could not walk, and could only sit with support. Cvostek and Trousseau signs were present.

Head CT scan disclosed similar lesions to those of 2007: massive, bilateral, symmetrical cerebellar calcifications in dentate, in the deep white matter near anterior horn of the lateral ventricles, and less pronounced calcifications, bilateral symmetric, in the mediane region of the nucleus lenticularis (Fig. 11-14).



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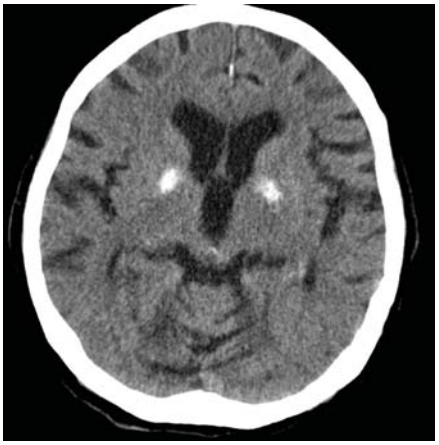
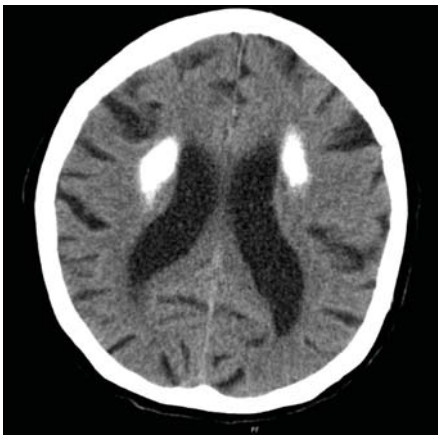


FIGURE 12



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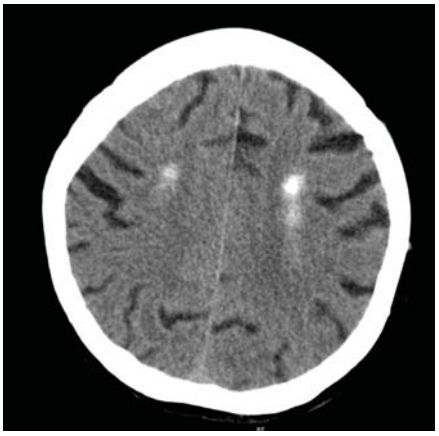

FIGURE 14

The bone window of the CT scan undoubtedly showed bone calcifications (Fig. 15, 16).

FIGURE 15

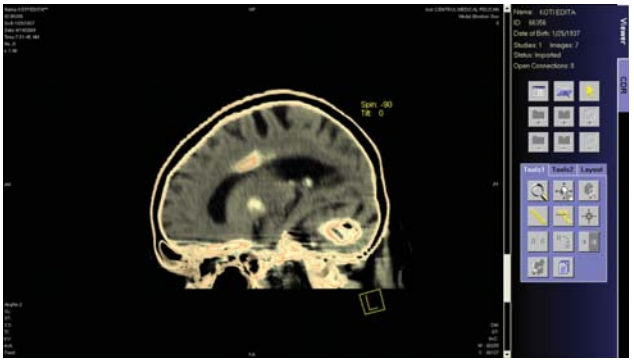

FIGURE 16

MRI did not bring additional findings. The lesions had no contrast enhancement. MRA with contrast disclosed bilateral ICA stenosis; the left one was very tight (Fig. 17).

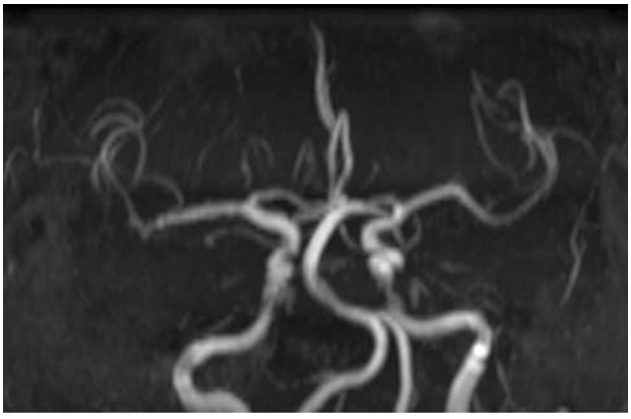

FIGURE 17

Laboratory findings showed a slightly elevated ESR, hypercholesterolemia, 235 mg/%, hypocalcaemia 5.6 mg%, normal magnesium serum level 2.55 mg%. Urine examination and renal function were normal. PTH level was decreased 5 pgm/l (normal ranges:10-65 pg/ml). Thyroid hormones were normal: T3 1.04 ng/ml, T4 9,29 μg/ml (normal values: 4,5-12/μg ml), TSH 1,20 μIU/ml (normal values: 0,49-4,67 μIU/ml).

Pelvic radiological examination showed diffuse demineralization and bilateral viciously consolidated fracture of the pubis. ECG showed rare ventricular ectopic beats and repolarisation alteration. Thyroid ultrasonography was normal. Doppler ultrasonography disclosed diffuse atherosclerotic lesions, with normal flow.

DISCUSSIONS

Physiological calcifications, frequently found in medical practice, were excluded in both cases (11). Both cases presented important neurological signs, in connection to the cerebral localization of the calcifications.

Decreased PTH level and hypocalcemia exclude other causes of intracerebral calcifications like: pseudohypoparathyroidism, hyperparathyroidism, monoxide carbon intoxication, encephalitis, Fahr disease, idiopathic basal ganglia calcifications, Cocayne syndrome, tuberous sclerosis, neurofybromatosis, vascular disease (vascular malformations, chronic ischemic or hemorrhagic stroke), cerebral parasitosis, aso (12-20).

Decreased calcium and increased phosphate serum level determines widespread symptomatic or asymptomatic intracerebral calcifications by uncompletely known mechanisms. Clinical signs may often be reversible once the calcium level gets into the normal range (1,2,3,4,5,21). Some clinical studies report that calcifications could even disappear by biphosphonate administration (22,23).

Hypoparathyroidism is frequently secondary, due to thyroidectomy, as in case1.

In case 2 hypoparathyroidism was primary. Other causes of hypoparathyroidism like: congenital (the onset was at age of 70 years), iatrogenic (no surgical or radiotherapy region was done upon the cervical region), tumoral or inflammatory parathyroid infiltration, sarcoidosis, aso were excluded.

Both patients had clinical signs of hypocalcemia: muscular cramps, Cvostek and Trousseau signs, those signs were recognized and a specific, but unfortunately inadequatelly treatment was initiated in case 1, and were ignored in case 2.

Patient 1 had had bilateral cataracts surgery, which could have been possibly linked to hypoparathyroidism (1, 2, 3, 4, 5).

Patient 2 had marked osteoporosis, viciously consolidated pelvic fracture, following a minor traumatic event by fall at the same level.

Both patients had important psychiatric features, frequently described in hypoparathyroidism (1, 2, 3, 4, 5, 22, 26). Nervousness, impaired concentration and memory disturbance were initially thought of as a consequence of hypocalcemia in case 1. Severe impairment : confusional episodes, hallucinations, were attributed to another cerebral disease, as their onset was associated with other neurological signs. Patient 2 had been treated with antidepressants several years before, with no improvement. She had had depressive state, anxiety, nocturnal insomnia, daytime somnolence in the last 10 years.

Both patients had emotional instability, memory impairment, fatigability, hyperexcitability, that were attributed to aging or to other kind of cerebral pathology (especially vascular).

Both patients had a lot of neurological features: extrapyramidal, pyramidal, balance and coordination impairment, dysarthria, dysphagia, signs that had been described in chronic hypoparathyroidism (1,2,3,4,5). They both presented motor deficit on admission and speech impairment was also present in case 2. We did not find the above mentioned symptoms in other reported studies. Imagistical studies did not disclose underlying vascular lesions causing aphasia, although the patient had vascular risk factors.

Predominance of symptoms on a hemibody was an interesting feature in both cases. The motor deficit, facial paresis, athetosis, numbness, tremor, all

had distinct right hemibody predominance in both cases. That kind of asymmetry of neurological signs and symptoms was frequently reported, although cerebral lesions, as evidenced by imagistical findings, were bilateral (4, 27).

None of the 2 patients had epileptic seizures, although seizures were reported as one of the most frequent cause of admission in a neurological department (1,2,3,4,5,13,28,29).

Calcium administration had a salutary effect in both cases. Clinical signs were markedly improved by normalization of calcium level, as it was reported in other studies (1,2,3,4,5,21).

The opportunity of bone metabolism acting medication would be settled according to endocrinological advise.

CONCLUSIONS

Association between neurological signs and intracerebral calcification requires an extremely complex management of calcium and phosphate metabolism, renal function, PTH level, and of a wide series of general and cerebral disease.

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